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(54) Title: INTRAMAMMARY INFUSION

(57) Abstract

An intramammary infusion comprises in a pharmaceutically acceptable vehicle a therapeutic or prophylactic dosage unit of a substance which is active against mammary infection and second, and optional subsequent, dosage units of active substance, particles of the said second and subsequent dosage units being microencapsulated within encapsulating membranes capable of degrading at preselected time intervals following administration.

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Intramammary Infusion

This invention relates to a veterinary intramammary infusion. More particularly, the invention relates to a therapeutic or prophylactic infusion for bovine mastitis, microbial mammary infection or similar problems which require intramammary introduction of medicaments.

A typical anti-mastitis dry cow (non-lactating) intramammary infusion would be a suspension in liquid paraffin of Cloxacillin Benzathine and Ampicillin Trihydrate. In general each infusion has effect over a period of around three weeks after administration. However, as the dry cow period is generally in excess of this, subsequent infusions are normally recommended. This is often inconvenient and costly. Furthermore if the cow should calve earlier than expected, shortly after infusion of the product, then the milk produced may continue to contain undesirable concentrations of the infusion for an unacceptable period. This, of course, may cause it to be deemed unfit for market and such milk would be subject to rejection, perhaps for some considerable time.

It is an object of this invention to obviate or mitigate the aforesaid disadvantages.

According to the present invention there is provided an intramammary infusion comprising in a pharmaceutically acceptable vehicle a therapeutic or prophylactic dosage unit of a substance which is active against mammary infection and second, and optional subsequent, dosage units of active substance, particles of the said second and subsequent dosage units being microencapsulated within encapsulating membranes capable of degrading at preselected time intervals following administration.

The microcapsules may be administered in a pharmaceutically acceptable vehicle in suspension capsules, mousse, liquid, paste, gel or the like. The active substance(s), together with any pharmaceutically acceptable additives, may be powdered or pelletted or similarly treated to facilitate delivery and microencapsulation.

A significant advantage obtained by utilising the infusion of the present invention is that it requires administration only once by a single infusion to obtain the full term of protection normally required. Additionally by containing the active substances within microcapsules of varying degradability, release of active substances may be controlled to provide a more uniform release profile. Most importantly the invention now provides a means of rapidly removing the drugs from the mammary system. In the event that a cow should calve and begin to lactate within the period of activity of the infusion, any residual active material may be removed within an acceptable period simply by milking the animal because the high milk yield after calving is adequate to achieve physical flushing out of the remaining intact microcapsules.

Preferably, the active substance is a mixture of Cloxacillin Benzathine and Ampicillin Trihydrate, the infusion being active for the treatment or prophylaxis of mastitis.

The encapsulating membrane may conveniently be selected from gelatin, an acrylate polymer, poly(DL-lactide-CO-glycolide) and poly(hydroxybutyrate). These materials are all commercially available and the choice of material will be made by selection depending upon the known degradation/dissolution rate. The degree of degradation required may be varied in a manner known per se in the art for other purposes.

The particle size of the microencapsulated material is believed to be non-critical provided that it is small enough to introduce into the udder intramammarily and not so small that it may obstruct milk-producing structures within the udder. Thus suitable particle sizes lie in the range of from about 10 µm to 500 µm. Preferred particle sizes lie in the range of from about 25 µm to about 250 µm, more preferably from about 45 µm to about 150 µm.

An example of an infusion of this invention is based on a formulation in which the first dosage unit is :

Cloxacillin Benzathine	1-1000 mg.
Ampicillin Trihydrate	1-1000 mg.

The said first dosage unit is in the form of a micronised powder which is encapsulated and dispersed in a sterile liquid paraffin vehicle. Also dispersed in the vehicle are three subsequent dosage units in which powder particles, the said Cloxacillin Benzathine and Ampicillin Trihydrate are microencapsulated for delayed release after three, six and nine weeks thus giving a total of twelve weeks effect.

It will be understood that the invention has been described with reference to drugs known to have therapeutic effect against bovine mastitis but is not intended to be restricted thereto. Those skilled in the art will appreciate that the invention may be applied as preventative or curative measure for the delivery of drugs other than those exemplified above and for the purpose of combatting other diseases of the mammary system in dry or lactating mammalian livestock. Likewise the physical form of the drug prior to microencapsulation is a matter of choice and it may be selected according to the characteristics of the drug required.

Claims

1. An intramammary infusion comprising, in a pharmaceutically acceptable vehicle, a therapeutic or prophylactic dosage unit of a substance which is active against mammary infection and second, and optional subsequent, dosage units of active substance, particles of the said second and subsequent dosage units being microencapsulated within encapsulating membranes capable of degrading at preselected time intervals following administration.

2. An intramammary infusion according to claim 1 wherein the microcapsules of active substance are in suspension in a pharmaceutically acceptable liquid vehicle.

3. An intramammary infusion according to claim 1 or claim 2 wherein the active substance is powdered prior to encapsulation.

4. An intramammary infusion according to any one of claims 1 to 3 wherein the active substance is a mixture of Cloxacillin Benzathine and Ampicillin Trihydrate, the infusion being active for the treatment or prophylaxis of mastitis.

5. An intramammary infusion according to any one of claims 1 to 4 wherein the particle size of the micro-encapsulated particles lies in the range of from 10 μm to 500 μm.

6. An intramammary infusion substantially as hereinbefore described.

7. A method of preparing an intramammary infusion comprising the steps of reducing at least one therapeutically-active substance to an administrable particle size, encapsulating the substance(s) in a degradable pharmaceutically acceptable encapsulation material to provide particles of therapeutically active substance(s)

within encapsulation membranes of varying degradation or dissolution rate and dispersing same in a sterile pharmaceutically acceptable vehicle.

8. A method of preparing an intramammary infusion according to claim 8 wherein the therapeutically active substance(s) is (are) reduced to a micronised powder prior to encapsulation.

9. A method according to claim 9 wherein the micro-capsules are dispersed in a sterile pharmaceutically acceptable liquid vehicle.

10. A method according to claim 9 or claim 10 wherein the active substance is a mixture of Cloxacillin Benzathine and Ampicillin Trihydrate, the infusion being active for the treatment or prophylaxis of mastitis.

11. A method according to any one of claims 7 to 10 wherein the particle size of the microencapsulated particles lies in the range of from 10 μm to 500 μm.

12. A method of treating a mammary disease in mammallian livestock comprising administering intramammarily an infusion comprising in a pharmaceutically acceptable vehicle a therapeutic or prophylactic dosage unit of a substance which is active against mammary infection and second, and optional subsequent, dosage units of active substance, particles of the said second and subsequent dosage units being microencapsulated within encapsulating membranes capable of degrading at preselected time intervals following administration.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 87/00625

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: A 61 K 9/22; A 61 D 1/02

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	A 61 D A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X Y	EP, A, 0076068 (BEECHAM GROUP PLC) 6 April 1983 see page 6, line 31 - page 7, line 15	1,2 3-11
Y	Biological Abstracts, no. 81040635, K.B. Singh et al.: "Clinical efficacy of orbenin LA and ampiclox LC in acute mastitis", see abstract, & Indian J. Vet. Med. 1984 (recd. 1985). vol. 4, no. 2, p. 94-96	4,10
Y	EP, A, 0132102 (SMITHKLINE BECKMAN CORP.) 23 January 1985 see page 6, line 1 - page 7, line 24; figure 1	3,5-11
A	US, A, 4011312 (REUTER et al.) 8 March 1977 see column 2, lines 24-60	5,11
A	Biological Abstracts, no. 9075320, A.B. Vilim et al.: "Microbiological ./.	

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
20th November 1987	16 DEC 1987
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	M. VAN MOL

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

	determination of penicillin G ampicillin and cloxacillin residues in milk", see abstract, & Journal of the Association of Official Analytical Chemists(USA) 1979, vol. 62, no. 6, p. 1247-1250 --------	4

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 12, because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv)
Methods for treatment of the human or animal body by means of surgery or therapy, as well as diagnostic methods.

2. [ ] Claim numbers....., because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. GB 8700625 SA 18537

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 01/12/87
The European Patent Office is is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0076068	06-04-83	JP-A- 58065156	18-04-83
		AU-A- 8867682	31-03-83
		US-A- 4472374	18-09-84
		CA-A- 1183082	26-02-85
EP-A- 0132102	23-01-85	AU-A- 2999284	17-01-85
		JP-A- 60036047	25-02-85
		US-A- 4564363	14-01-86
		CA-A- 1223817	07-07-87
US-A- 4011312	08-03-77	CA-A- 1046939	23-01-79